TITLE AMENDMENTS:

Replace the title with:

IMMUNOSUPPRESSIVE IMIDAZOLE DERIVATIVES AND THEIR COMBINATION PREPARATIONS WITH TACROLIMUS OR CYCLOSPORINS

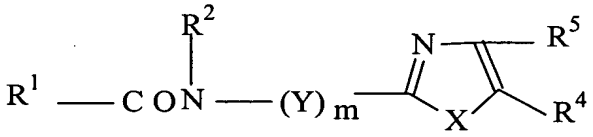
SPECIFICATION AMENDMENTS

Replace paragraph [0009] with:

[0009] In the present invention, the "compound possessing an inhibitory activity on the production of nitric oxide" should not be limited and be considered to mean any compounds which have an inhibitory activity on the production of nitric oxide. ~~Preferable~~ A preferable one is a compound possessing an inhibitory activity on the production of inducible nitric oxide synthase (iNOS), and ~~the other~~ another preferable one is a compound possessing an iNOS-inhibitory activity.

Replace paragraph [0010] with:

[0010] The compound having the following formula (I) are exemplified as a preferable example of the above "compound possessing an inhibitory activity on the production of nitric oxide".



(I)

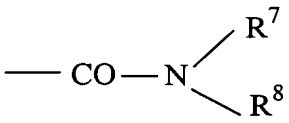
wherein

R^1 is indolyl which may have a suitable substituent selected from the group consisting of lower alkyl, phenyl, halogen, lower alkoxy, and nitro, benzofuranyl, phenyl which may have one or two suitable substituent(s) selected from the group consisting of amino, acylamino, lower alkylamino, halogen, lower alkoxy and nitro, lower alkyl, quinoxalinyl, quinolyl, pyrrolyl, pyrimidinyl having benzofuranyl, benzimidazolyl, benzothienyl, benzothiazolyl, benzoxazolyl, indolinyl, anilino, phenylcarbamoyl or imidazolyl which may have one or two suitable substituent(s) selected from the group consisting of phenyl, lower alkyl and indolyl;

R^2 is hydrogen or phenyl(lower)alkyl;

R^4 is hydrogen, phenyl or pyridyl, each of which may have suitable substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halogen, trihalomethyl, nitro, cyano, imidazolyl, optionally protected hydroxy, acyl, amino, acylamino, diacylamino, di(lower)alkyl-amino, amino(lower)alkyl, acylamino(lower)alkyl, pyrazolyl, morpholinyl, piperidyl, triazolyl, lower alkoxy(lower)alkoxy, hydroxy(lower)alkyl, lower alkylpiperazinyl, phenyl and carboxy, quinolyl or 3,4-methylenedioxyphenyl;

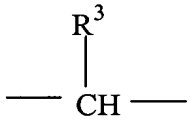
R^5 is hydrogen, imidazolyl, phenyl, nitrophenyl, phenyl(lower)- alkyl, optionally esterified carboxy or a group of the formula:



in which R^7 and R^8 are the same or different and each is hydrogen, phenyl, phenyl(lower)alkyl, lower alkyl or lower alkoxy; or R^4 and R^5 in combination form a group of the formula:

-CH=CH-CH=CH-

Y is a group of the formula:

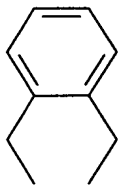


in which R^3 is hydrogen or a group of the formula:

~~-(CH2) n-R6~~ $\underline{-(CH_2)_n-R^6}$

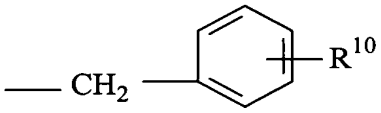
in which R^6 is optionally protected hydroxy, acyl, carboxy, acylamino, lower alkoxy, phenyl(lower)alkoxy, lower alkylthio, phenyl which may have a suitable substituent selected from the group consisting of lower alkoxy, halogen, amino, acylamino, diacylamino and nitro, pyridyl which may have a suitable substituent selected from the group consisting of lower alkoxy and halogen, pyrazinyl, pyrimidinyl, furyl, imidazolyl, naphthyl, N-(lower)alkylindolyl or 3,4-methylenedioxyphenyl, and n is an integer of 0 to 3, or a group of the formula:

in which R^{11} is phenyl, phenoxy or phenyl(lower)alkoxy; or R^2 and R^3 in combination form a group of the formula:



m is O or 1; and
X is S or NR^9

in which R^9 is hydrogen, lower alkyl, cyclo(lower)alkyl or a group of the formula:



in which R^{10} is hydrogen, lower alkyl or lower alkoxy; or a pharmaceutically acceptable salt thereof.

Replace paragraph [0014] with:

[0014] Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkylthio", "lower alkylthio(lower)alkyl", "N-(lower)alkylindolyl", "lower alkylamino", di(lower)alkyl-amino", "phenyl(lower)alkyl", "amino(lower)alkyl", "acylamino-(lower)alkyl", "hydroxy(lower)alkyl" and "lower alkyl-piperazinyl" include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which a more preferred one is C1-C4 alkyl.

Replace paragraph [0015] with:

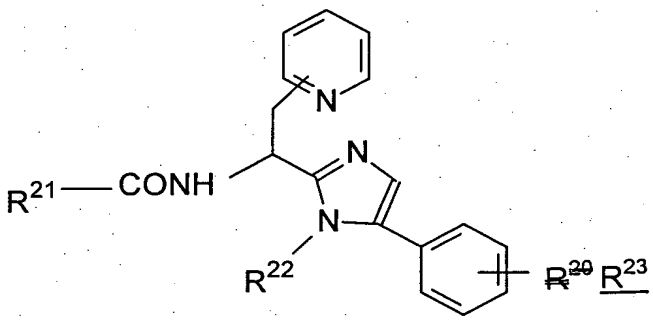
[0015] Suitable "lower alkoxy" and "lower alkoxy moiety" in the terms "lower alkoxy(lower)alkoxy" and "phenyl(lower)alkoxy" include, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, in which a more preferred one is C1-C4 alkoxy.

Replace paragraph [0018] with:

[0018] Suitable "trihalomethyl" includes, for example, trifluoromethyl, trichloromethyl and tribromomethyl, in which a preferred one is trifluoromethyl.

Replace paragraph [0026] with:

[0026] And further, the compound having the following formula (II) is also exemplified as the preferable one of the "compound possessing an inhibitory activity on the production of nitric oxide".



(II)

wherein,

R^{21} is benzofuranyl having halogen,

R^{22} is lower alkyl, and

R^{23} is morpholinyl.

Replace paragraph [0037] with:

[0037] ~~Preferable~~ Preferably, R^{24} may be a cyclo(C_{5-7})alkyl group, and the following ones can be exemplified.

(a) a 3,4-di-oxo-cyclohexyl group;

(b) a 3-R^{20}-4-R^{21}-cyclohexyl group, in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a -$OCH_2OCH_2CH_2OCH_3$ group, and

R^{21} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a -$OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy,

or $R^{25}R^{26}CHCOO$-, in which R^{25} is optionally protected hydroxy or protected amino, and

R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; or

(c) cyclopentyl group substituted by methoxymethyl, optionally protected

hydroxymethyl, acyloxymethyl (in which the acyl moiety optionally contains either a methylamino group which may be quaternized, or a carboxy group which may be esterified), one or more amino and/or hydroxy groups which may be protected, or aminooxalyloxymethyl. A preferred example is a 2-formyl-cyclopentyl group.

Replace paragraph [0046] with:

[0046] Examples of the aliphatic acyl groups substituted by an aromatic group include ~~ar(lower)alkanoyl~~ a (lower)alkanoyl group optionally having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2 phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

Replace paragraph [0049] with:

[0049] The ~~tieyelie~~ tricyclic compounds (III) and its pharmaceutically acceptable salt for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs-host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059, etc.].

Replace paragraph [0078] with:

[0078] The murine macrophage cell line RAW264.7 (American Type Culture Collection, No. TIB71) was used in this study. RAW264.7 cells were grown on F75 plastic culture flasks at 37°C, 5% in Dulbecco's modified Eagle's medium (DMEM) supplemented with L-glutamine, penicillin, streptomycin and 10% heat-inactivated fetal bovine serum. They were removed from culture flasks by rubber cell scraper and were centrifuged and resuspended in DMEM without phenol red. They were plated in 96-well microtiter plates (10^5 cells per well) and allowed to adhere over 2 hours. The test samples were added and the cells were preincubated for 1 hour. Thereafter the cells were activated with both of lipopolysaccharide (LPS) (1μg/ml) and interferon γ (INF γ) (3 u/ml) for 18-24 hours. An equal volume of Griess reagent (1% sulfanilamide/0.1% N-naphthylethylenediamine dihydrochloride/2.5% ~~H3PO4~~ H_3PO_4) was added and the cells were incubated at room

temperature for 10 minutes. The absorbance was read at 570 nm using microplate reader and ~~NO2-~~ NO_2 was measured using ~~NaNO2~~ $NaNO_2$ as a standard.

Test result:

Test compound (10^{-5}M)	Inhibition (%)
(a)	100
(b)	100
(c)	100
(d)	100
(e)	100
(f)	100
(g)	100